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Short Communication

Contraindication of live vaccines in immunocompromised patients: an estimate of the number of affected people in the USA and the UK

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Live attenuated vaccines (LAVs) offer strong cellular and antibody responses for protecting at-risk populations from severe infectious diseases.[1] Examples include the measles, mumps, herpes zoster, varicella, and yellow fever vaccines. LAVs, however, are usually contraindicated for individuals with immunocompromising (IC) conditions because of a low risk, based on clinical evidence or theoretical considerations, that the partially attenuated vaccine strain could revert to the wild-type form and cause disease.[2–4] At the same time, individuals with IC conditions need vaccines because they are at an increased risk of severe infections.[5–7] In cases where alternatives to live vaccines are not available for individuals with IC conditions, the risk of potential adverse events from the vaccine must be weighed against the risk of disease from the wild-type pathogen.

To make informed decisions about developing or offering alternative vaccines to people with IC conditions, an estimate of the size of the IC population is needed. The only estimate to date, published in 2001, suggested that close to 10 million individuals in the USA or 3.6% of the population had IC conditions, although the authors explained that this was a 'back of the envelope' calculation based solely on the sum of the numbers of organ transplants, individuals with diagnosed and undiagnosed human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) and patients with cancer.[8]

To better understand the unmet need for alternative vaccines in the adult IC population, we estimated the total burden of 11 main IC conditions listed as contraindicated conditions in international vaccination guidelines and recommendations.[9–12] The GLOBOCAN database[13] was used for cancer incidence and prevalence rates. For all other IC conditions, incidence and prevalence rates were obtained by a search of PubMed and, where data were unavailable, by a search for surveillance data available online (Table 1). When more than one source of data with the necessary age stratification (18+ years) was available, we selected the one with the highest quality, most representative data using a tool adapted from the Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies.[14]

Although our initial goal was to make estimates for 10 countries, our search of peer-reviewed articles and surveillance databases yielded sufficient data only for the USA and UK. Based on the data we collected, we estimated that in 2012, 7.6 million adults (≥18 years old) in the USA and 1.7 million adults in the UK had one of the IC conditions listed in Table 1.

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Table 1 – Incidence and prevalence of IC conditions in adults in the USA and UK.

IC condition[a]	Measure	USA			UK		
		No. per 100,000 persons or person-years	Year	Estimated no. of cases[b]	No. per 100,000 persons or person-years	Year	Estimated no. of cases[c]
Solid organ malignancies	Prevalence	362.05[d]	2012	869,593	320.79[d]	2012	160,977[e]
	Incidence	460.57[d]	2012	1,106,224	443.29[d]	2012	222,448
Haematological malignancies	Prevalence	35.14[d]	2012	84,401	33.31[d]	2012	16,715
	Incidence	50.41[d]	2012	121,078	48.91[d]	2012	24,543
Psoriasis	Prevalence	883[f]	1996–2009	2,120,842	1520.2[g]	1987–2002	919,502[e]
	Incidence	78.9[h]	1970–1999	191,065[e]	140[i]	1996–1997	72,029[e]
Systemic lupus erythematosus	Prevalence	143.75[j]	2000–2004	512,016[e]	49.31[k]	1998	24,746[e]
	Incidence	7.22[l]	2003–2008	18,127[e]	3.02[k]	1992–1998	1,789[e]
Rheumatoid arthritis	Prevalence	720[m]	1995–2007	1,729,339	570[n]	2010	286,029
	Incidence	40.9[m]	1995–2007	99,195[e]	48[o]	1990–1995	20,881[e]
Crohn's disease	Prevalence	96.3[p]	2002	308,683[e]	157[q]	2007	78,784
	Incidence	6.3[p]	1996–2002	18,067[e]	9.56[q]	2003–2007	4,725[e]
Ulcerative colitis	Prevalence	155.8[p]	2002	514,792[e]	243[r]	2002	121,939
	Incidence	12.0[p]	1996–2002	36,496[e]	ND	ND	ND
HIV/AIDS	Prevalence	324.6[s]	2009	830,101[e]	150[t]	2012	75,271
	Incidence	19.5[s]	2010	48,248[e]	10[t]	2012	5018
HSCT	Prevalence	ND	ND	ND	ND	ND	ND
	Incidence	4.0[u]	2006	9,607[e]	ND	ND	ND
Solid organ transplant	Prevalence	ND	ND	ND	ND	ND	ND
	Incidence	10.9	2012	26,281[v]	9.27	2013–2014	4,655[e,w]
End-stage renal disease	Prevalence	190.09[x]	2011	650,483[e]	86.32[y]	2011	55,624[e]
	Incidence	35.71[x]	2011	123,125[e]	10.70[z]	2011	6,944[e]
Total	**Prevalence**	–	–	**7,620,252**	–	–	**1,739,587**
	Incidence	–	–	**1,797,512**	–	–	**363,031**

The GLOBOCAN database was used for cancer incidence and prevalence rates. For all other IC conditions, peer-reviewed articles in English published in the last 5 years were identified by a search of PubMed on October, 2013 using the following search string: [IC condition] AND (incidence OR prevalence) AND [country]. When more than one publication was found with the necessary age stratification (18+ years), data from the highest quality study were selected using a tool adapted from the Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies (http://www.ephpp.ca/tools.html). When data were not found in the initial search, the search was extended to the last 10 years. If data were still not found, they were obtained from online global surveillance databases when available, or if not, from country-specific surveillance databases identified using the Google search engine. Abbreviations: HIV/AIDS, human immunodeficiency virus/acquired immune deficiency syndrome; HSCT, haematopoietic stem cell transplant; ND, no data; Ref, reference; No: number; IC: immunocompromising.

[a] Included conditions were based on: Habel et al. *Cancer Epidemiol Biomarkers Prev*. 2013;**22**:82–90; US Centers for Disease Control and Prevention. CDC Health Information for International Travel 2014. New York: Oxford University Press; 2014; Lupus Canada. Immunosuppressive drugs used in treating lupus. 2007. Available from http://www.lupuscanada.org/pdfs/factsheets/Immuno-Online.pdf; Trevillian P. *Australian Prescriber*. 2006;**29**:102–8; Centers for Disease Control and Prevention. *MMWR Recomm Rep*. 1993;**42**:1–18; Centers for Disease Control and Prevention. *MMWR Recomm Rep*. 2011;**60**:1–64; Fiore et al. *MMWR Recomm Rep*. 2010; **59**:1–62; and Harpaz et al. *MMWR Recomm Rep*. 2008;**57**:1–30.

[b] Based on the 2012 adult population in the USA (240,185,952). Source: http://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?src=bkmk.

[c] Based on the 2012 adult population in the UK (50,180,600). Source: http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk–england-and-wales–scotland-and-northern-ireland/mid-2011-and-mid-2012/rft—mid-2012-uk-population-estimates.zip.

[d] International Agency for Research on Cancer. GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx.

[e] Cases presented are based on age-standardized rates, which were calculated based on 2012 population data using age-specific rates reported (where available) and the 2012 census data to estimate the cases for the ≥18 years old population.

[f] Asgari et al. *Pharmacoepidemiol Drug Saf*. 2013;**22**:842–9.

[g] Gelfand et al. *Arch Dermatol*. 2005;**141**:1537–41.

[h] Icen et al. *J Am Acad Dermatol*. 2009;**60**:394–401.

[i] Huerta et al. *Arch Dermatol*. 2007;**143**:1559–65.

[j] Feldman et al. *Arthritis Rheum*. 2013;**65**:753–63.

[k] Nightingale et al. *Pharmacoepidemiol Drug Saf*. 2006;**15**:656–61.

[l] Furst et al. *Lupus*. 2013;**22**:99–105.

[m] Myasoedova et al. *Arthritis Rheum*. 2010;**62**:1576–82.

[n] Jordan et al. *Ann Rheum Dis*. 2014;**73**:212–8.

[o] Humphreys et al. *Ann Rheum* Dis. 2013;**72**:1315–20.

[p] Herrinton et al. *Am J Gastroenterol*. 2008;**103**:1998–2006.

[q] Steed et al. *Scott Med J*. 2010;**55**:22–5.

[r] Stone et al. *Eur J Gastroenterol Hepatol*. 2003;**15**:1275–80.

[s] Prejean et al. *J Community Health*. 2013;**38**:414–26.

[t] Aghaizu et al. HIV in the United Kingdom: 2012 Report. London: Public Health England; 2012. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/326601/HIV_annual_report_2013.pdf.

[u] Gratwohl et al. *JAMA*. 2010;**303**:1617–24.
[v] Transplants in the U.S. by Recipient Age, 2012; Based on OPTN data as of August 1, 2015. Available from: http://optn.transplant.hrsa.gov/converge/latestData/step2.asp.
[w] Transplant activity report (2014–2015) Table 2.4, Page 10. Available from: http://nhsbtmediaservices.blob.core.windows.net/organ-donation-assets/pdfs/activity_report_2014_15.pdf.
[x] U.S. Renal Data System. USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health; 2013. Available from: http://www.usrds.org/atlas.aspx.
[y] Shaw et al. *Nephron Clin Pract*. 2013; **125**:29–53.
[z] Gilg et al. *Nephron Clin Pract*. 2013; **125**:1–27.

This represents 3.17% of the total adult population in the USA and 3.47% of the total adult population in the UK. Each year, there are an estimated 1.8 million new cases of IC conditions in the USA and 0.36 million in the UK.

These estimates are subject to differences in case ascertainment, not to mention differences in data collection and reporting for each condition. For example, the incidence and prevalence rates for psoriasis were twice as high in the UK as in the USA. Possible explanations are differences in case ascertainment, demographics, geography, methodology, case definitions and definitions of prevalence. In addition, we used only a single data source for incidence or prevalence in each country; using alternative sources, especially for the more dominant IC conditions like HIV/AIDS and malignancies, could have some effect on the estimates. Regardless, the numbers for the IC population in the USA are in line with the previous estimates,[8] and the overall prevalence of IC conditions is similar for the USA and UK, suggesting that our estimates are reasonable.

Not all subjects with chronic conditions like systemic lupus erythematosus, psoriasis, rheumatoid arthritis and inflammatory bowel disease will be on immune-suppressive treatments at any point in time, but little data is available to determine the corresponding proportions. Similarly, for HIV/AIDS, not all subjects will be immunosuppressed at any given time (i.e. CD4 counts <200) and, again, the proportion is difficult to determine from available data. To help address this limitation, we tested a scenario in which half of patients with these conditions are considered immunosuppressed at any given time. Based on this assumption, and using the unaltered estimates for the remaining conditions, the estimated number of adults with IC conditions was 4.6 million in the USA (1.92%) and 1.0 million in the UK (1.97%).

These estimates are only a first step in understanding how many individuals with IC conditions require alternative vaccines. Many other variables must be considered, notably, the cause and severity of immunosuppression for each IC condition, which can vary greatly,[15] and for individuals receiving immunosuppressive treatments, the level and duration of immunosuppression for which LAVs should be contraindicated. In addition, the nature of each infectious disease, the risk of exposure to it and its associated morbidity must be considered when determining who should or should not receive LAVs.

In summary, despite the limitations to our analysis and lack of data for countries other than the USA and the UK, our calculations suggest that roughly 2–3% of the global adult population lives with an IC condition and might benefit from alternative vaccines to LAVs. This estimate is meant as a starting point for understanding the magnitude of the need for alternatives to LAVs. Although the numbers and percentages appear to be reasonable for the UK and the USA, and therefore perhaps also for upper-income countries in general, they may not be accurate for individual countries, especially lower-income countries. Analyses of large datasets, coupled with harmonized case ascertainment and data collection, as well as additional country-specific data on disease burden are needed to make more accurate estimates.

Author statements

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Ethical approval

Not required as no patient were directly involved in the study.

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Competing interests

LV, DC, AG and GC are employees of the GSK group of companies. DC hold stock and GC hold stock and shared options from the GSK group of companies. At the time of the study, AO was employed by the GSK group of companies. He is currently an employee of Alexion Pharmaceuticals GmbH. EB, HV and FvK received grants from the GSK group of companies under and outside the submitted.

Author contributions

AO, AG, DC, GC, EB, HV and FvK participated to the conception/design of the study. AO, AG, DC, LV, EB, HV and FvK participated to the acquisition/collection of data. AO, AG, DC,

GC, LV, EB, HV and FvK performed the analysis. AO, AG, DC, GC, EB, HV and FvK participated to the interpretation of the results. DC and LV provided statistical expertise.

REFERENCES

1. Minor PD. Live attenuated vaccines: historical successes and current challenges. *Virology* 2015;**479–480**:379–92.
2. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis* 2014;**58**:309–18.
3. Lauring AS, Jones JO, Andino R. Rationalizing the development of live attenuated virus vaccines. *Nat Biotechnol* 2010;**28**:573–9.
4. Lobermann M, Borso D, Hilgendorf I, Fritzsche C, Zettl UK, Reisinger EC. Immunization in the adult immunocompromised host. *Autoimmun Rev* 2012;**11**:212–8.
5. McDonald JR, Zeringue AL, Caplan L, Ranganathan P, Xian H, Burroughs TE, et al. Herpes zoster risk factors in a national cohort of veterans with rheumatoid arthritis. *Clin Infect Dis* 2009;**48**:1364–71.
6. Wong A, Marrie TJ, Garg S, Kellner JD, Tyrrell GJ. Increased risk of invasive pneumococcal disease in haematological and solid-organ malignancies. *Epidemiol Infect* 2010;**138**:1804–10.
7. Winthrop KL. Risk and prevention of tuberculosis and other serious opportunistic infections associated with the inhibition of tumor necrosis factor. *Nat Clin Pract Rheumatol* 2006;**2**:602–10.
8. Kemper AR, Davis MM, Freed GL. Expected adverse events in a mass smallpox vaccination campaign. *Eff Clin Pract ECP* 2002;**5**:84–90.
9. Centers for Disease Control and Prevention. Recommendations of the Advisory Committee on Immunization Practices (ACIP): use of vaccines and immune globulins for persons with altered immunocompetence. *MMWR Recomm Rep* 1993;**42**:1–18.
10. Centers for Disease Control and Prevention. General recommendations on immunization – recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2011;**60**:1–64.
11. Fiore AE, Uyeki TM, Broder K, Finelli L, Euler GL, Singleton JA, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Recomm Rep* 2010;**59**:1–62.
12. Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2008;**57**:1–30. quiz CE2–4.
13. International Agency for Research on Cancer. *GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012*; 2014. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx.
14. Project EPHP. *Quality assessment tool for quantitative studies*; 2009 [27 Jun 2016]. Available from: http://www.ephpp.ca/tools.html.
15. O'Shea D, Widmer LA, Stelling J, Egli A. Changing face of vaccination in immunocompromised hosts. *Curr Infect Dis Rep* 2014;**16**:420.